Passive Smoking and Lung Cancer in Nonsmoking Women

Ross C. Brownson, PhD, Michael C. R. Alavanja, DrPH, Edward T. Hock, BS, and Timothy S. Loy, MD

ABSTRACT

Objectives. The causes of lung cancer among nonsmokers are not clearly understood. To further evaluate the relation between passive smoke exposure and lung cancer in nonsmoking women, we conducted a population-based, case-control study.

Methods. Case patients (n = 618), identified through the Missouri Cancer Registry for the period 1986 through 1991, included 432 lifetime nonsmokers and 186 ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year. Control subjects (n = 1402) were selected from driver's license and Medicare files.

Results. No increased risk of lung cancer was associated with childhood passive smoke exposure. Adulthood analyses showed an increased lung cancer risk for lifetime nonsmokers with exposure of more than 40 pack-years from all household members (odds ratio [OR] = 1.3; 95% confidence interval [CI] = 1.0, 1.8) or from spouses only (OR = 1.3; 95% CI = 1.0, 1.7). When the time-weighted product of pack-years and average hours exposed per day was considered, a 30% excess risk was shown at the highest quartile of exposure among lifetime nonsmokers.

Conclusions. Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and worksites are well-advised. (*Am J Public Health.* 1992;82:1525–1530)

Introduction

Although most lung cancer occurs in smokers, approximately 9% to 13% of lung cancer cases in US women develop in lifetime nonsmokers.[1–5] The causes of lung cancer in nonsmokers have not been widely studied, but probably comprise a diverse set of factors including genetics, occupational factors, radon exposure, diet, and a history of nonmalignant lung disease.

In addition to these risk factors, the etiologic role of passive smoke exposure has received increasing scrutiny over the past decade. Numerous studies[5–20] have suggested an elevation in lung cancer risk for nonsmoking females who live with a smoker, with a summary excess risk of approximately 30%.[21,22] However, several recent studies[1,23–27] have shown no increased lung cancer risk due to spousal smoking.

Limited evidence[7,26] also suggests that exposure to passive smoke in childhood may increase risk of lung cancer. For example, a recent case-control study from New York found that household exposure to tobacco smoke during childhood of 25 or more smoker-years' duration was associated with a doubling of lung cancer risk.[26]

Most previous studies of passive smoking and lung cancer, although suggestive of a positive effect, have had several deficiencies. These deficiencies include sample sizes insufficient to singly demonstrate significant elevations in risk, limited data on passive smoke exposure in both childhood and adulthood, and lack of histologic review of cases to verify lung cancer diagnosis and to allow analyses by cell type.

To more fully evaluate the relationship between lung cancer and passive smoke exposure in childhood and adulthood, we conducted a large case-control study of lung cancer among nonsmoking women.

Methods

Case Group

Case patients were identified through the Missouri Cancer Registry, which is maintained by the Missouri Department of Health. The Registry began collecting data on incident cancer cases from public and private hospitals in 1972, and hospital reporting was mandated by law in 1984. Registry reporting procedures have been discussed in more detail elsewhere.[28] To ensure complete reporting of lung cancer cases in women for the current study, we had Registry staff complete special case ascertainment visits to participating hospitals. The case series included White Missouri women, aged 30 to 84 years, who were diagnosed with primary lung cancer between January 1986 and June 1991. Selection was limited to Whites because of small numbers of other racial/ethnic

Ross C. Brownson is with the Division of Chronic Disease Prevention and Health Promotion, Missouri Department of Health, Columbia, Mo. Michael C. R. Alavanja is with the Epidemiology and Biostatistics Program, National Cancer Institute, Rockville, Md. Edward T. Hock is with Information Management Services, Rockville, Md. Timothy S. Loy is with the Pathology Department, University of Missouri School of Medicine, Columbia, Mo.

Requests for reprints should be sent to Ross C. Brownson, PhD, Division of Chronic Disease Prevention and Health Promotion, Missouri Department of Health, 201 Business Loop 70 West, Columbia, MO 65203.

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groups. The case group included both lifetime nonsmokers and ex-smokers who had stopped smoking at least 15 years before diagnosis or who had smoked for less than 1 pack-year. From the 3475 cases of lung cancer in women reported for the study period, 650 eligible patients were identified. Physicians denied interview permission for 24 (4%) of these patients and an additional 8 women (1%) refused to be interviewed. The final case group included 432 (70%) lifetime nonsmokers and 186 (30%) ex-smokers. Of the 618 case interviews, 216 were conducted with patients themselves and 402 were conducted with surrogates because the patient was too ill to be interviewed or had died. Of the surrogate interviews, 105 (26%) were conducted with the patient's spouse and 297 (74%) were conducted with another relative (e.g., offspring or sibling).

Histologic Confirmation of Cases

Tissue slides were reviewed for histologic verification for 468 (76%) of the 618 cases. Slides for these cases were examined simultaneously by three pathologists (T.L., E.I., and J.M.) using a multiheaded microscope without knowledge of the referring pathologist's diagnosis. In surgical specimens, consensus diagnoses were obtained with the criteria outlined in the World Health Organization classification scheme.[29] When only cytologic material was available, consensus was obtained with standard cytologic criteria.[30]

Control Group

A population-based sample of control subjects was ascertained by two methods. For women younger than 65 years, a sample of state driver's license files was provided by the Missouri Department of Revenue. For women aged 65 to 84 years, control subjects were generated from the Health Care Finance Administration's roster of Medicare recipients.[31] On the basis of age distribution of lung cancer cases previously reported to the Registry, the final control group was matched by age group to case patients at an approximate 2.2 to 1 ratio. All control subjects were interviewed directly. Of the 1862 potentially eligible control subjects, 335 (18%) refused the initial screening interview and 125 (7%) of those screened and found eligible refused the full interview. The final control group numbered 1402.

Questionnaire Design and Administration

Telephone interviews were conducted by trained interviewers. The first phase of the interview consisted of a screening questionnaire to verify the age, race, and smoking status of case patients and control subjects. For subjects who were screened and found eligible and who agreed to the full interview, the study questionnaire consisted of sections on residential history, passive smoke exposure, personal health history, family health history, reproductive history, occupational exposure, and dietary factors.

Questions regarding passive smoking focused on exposure in both childhood (17 years and younger) and adulthood (18 years and older). For each time period, respondents were questioned about the source of exposure (e.g., a parent or spouse). After an individual source was determined, a series of detailed questions were asked on the type of tobacco used, duration of exposure, intensity of exposure, and average number of hours per day exposed. These questions were partially modeled after those developed by Wynder et al.[32] In addition to quantitative estimates of exposure, respondents were asked to estimate a perceived level of exposure during childhood and adulthood ("During most of your adult years, would you say that your average exposure to smoke at home was light, moderate, or heavy?").

Analyses

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with multiple logistic regression.[33] The linearity of trends in risk according to level of passive smoke exposure was evaluated with Mantel's one-tailed test.[34] We initially examined numerous potential confounding factors. These included age, active smoking (for ex-smokers), history of previous lung diseases, dietary beta carotene, and dietary fat. Of these variables, only age, active smoking, and previous lung disease appeared to confound passive smoking findings; therefore, the results presented are adjusted for these factors.

Histologic type-specific analyses were conducted for cases for which consensus diagnoses were determined. These analyses were undertaken because earlier studies[5,18,20] have shown variations in risk by cell type, and biological mechanisms have been proposed that might account for these variations.[20,35]

Results

Sociodemographic and smoking-related characteristics of case patients and control subjects have been presented in detail elsewhere.[36] In brief, the average ages of case patients and control subjects were 71.5 years and 69.9 years, respectively. The two groups were also comparable on level of education and income. Among ex-smokers, the median interval since cessation was 24 years, and average smoking intensity was 16.4 cigarettes per day.

There was little evidence of increased lung cancer risk associated with passive smoke exposure in childhood (Table 1). This lack of association was apparent for both the dichotomous variables (never vs ever exposed) and quantitative measures such as pack-years. The only suggestion of elevated risk was noted for less quantitative exposure variables (not shown in table). Among lifetime nonsmokers, an increased risk of lung cancer was shown for those reporting moderate (OR = 1.7; 95% CI = 1.1, 2.5) and heavy (OR = 2.4; 95% CI = 1.3, 4.7) exposure to passive smoke in childhood. Risk estimates for most childhood exposure variables were slightly higher (approximately 20% to 30%) when analyses included only direct interviews, although none achieved statistical significance.

An elevated risk of lung cancer was identified for lifetime nonsmokers at the highest quartile of passive smoke exposure in adulthood (Table 2). At an exposure level of more than 40 pack-years, lifetime nonsmokers showed a 30% increase in risk whether the source of exposure was all household members or spouses only. Similarly, when the product of pack-years and average number of hours exposed per day was considered, lung cancer risk for lifetime nonsmokers was elevated for the highest exposure quartile whether the source was all household members (OR = 1.3; 95% CI = 1.0, 1.8) or spouses only (OR = 1.3; 95% CI = 1.0, 1.7). Among lifetime nonsmokers, a positive increasing trend in risk was noted for pack-years ($P = .06$). Passive smoking–related risk estimates for adulthood exposures were slightly lower for all subjects (i.e., both ex-smokers and lifetime nonsmokers) than for lifetime nonsmokers alone, although the same general elevations in risk were noted. When analyses were limited to direct interviews, no clear pattern of increase or decrease in risk estimates was apparent. Regarding less quantitative exposure variables, elevated risk was shown for all subjects (OR = 1.7; 95% CI = 1.1, 2.6) and for lifetime nonsmok-

TABLE 1—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Childhood and Lung Cancer in Women, Missouri, 1986 through 1991

Source of Exposure	All Subjects[b]				Lifetime Nonsmokers			
	No. Cases	No. Controls	OR	95% CI	No. Cases	No. Controls	OR	95% CI
All household members								
Never	430	928	1.0		323	802	1.0	
Ever	185	472	0.8	0.7, 1.1	106	364	0.8	0.6, 1.1
Cigarette pack-years								
0	430	928	1.0		323	802	1.0	
>0–15	42	129	0.7	0.5, 1.0	27	104	0.7	0.4, 1.1
>15–25	31	119	0.6	0.4, 0.9	20	91	0.6	0.4, 1.0
>25	34	117	0.7	0.4, 1.1	21	87	0.7	0.4, 1.2
Parents only								
Never	489	1021	1.0		357	877	1.0	
Ever	126	379	0.7	0.5, 0.9	74	289	0.7	0.5, 0.9
Cigarette pack-years								
0	489	1021	1.0		357	877	1.0	
>0–15	19	90	0.4	0.3, 0.7	12	70	0.5	0.2, 0.8
>15–25	27	118	0.5	0.3, 0.7	17	87	0.5	0.3, 0.9
>25	33	99	0.7	0.5, 1.1	21	74	0.8	0.5, 1.4

[a]Adjusted for age, history of previous lung disease, and active smoking (all subjects only).
[b]Includes lifetime nonsmokers and ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year.

ers (OR = 1.8; 95% CI = 1.1, 2.9) who reported heavy exposure to passive smoke.

In general, there was no elevated lung cancer risk associated with passive smoke exposure in the workplace (not shown in table). Only lifetime nonsmokers showed a slight increase in risk at the highest quartile of workplace exposure (OR = 1.2; 95% CI = 0.9, 1.7).

Among the 468 lung cancers that were verified histologically, the predominant cell types were adenocarcinoma (62.4%), other/mixed cell types (25.2%), squamous cell carcinoma (5.8%), bronchioalveolar carcinoma (4.1%), and small cell carcinoma (2.5%). The other/mixed cell type category consisted mainly of large cell lung cancers, though, these lacked sufficient pathologic evidence for precise classification. Table 3 presents results of cell type–specific analyses for adulthood exposures. Elevated risk was shown for other/mixed cell types at more than 40 pack-years of exposure (OR = 1.6; 95% CI = 1.0, 2.5). Although it was based on small numbers, a risk estimate of 1.7 was observed for small cell carcinoma at the highest level of exposure.

We also examined risk among women who had been exposed to passive smoke in both childhood and adulthood, in childhood but not in adulthood, and in adulthood but not in childhood. There was no evidence of interaction between exposure during the two periods.

Discussion

Our study suggests that exposure to high levels of environmental tobacco smoke in adulthood increases the risk of lung cancer in nonsmokers. Exposure of more than 40 pack-years' duration increased the risk of lung cancer among nonsmokers by approximately 30%. This relationship was consistently demonstrated among lifetime nonsmokers whether the exposure variable was pack-years or the time-weighted product of pack-years and average number of hours exposed per day. Our findings are similar to those of another large study of lung cancer in nonsmoking women[20] that identified an OR of approximately 1.3 due to exposure to greater than 40 pack-years of spousal smoking.

In earlier studies, the most commonly reported index of passive smoking exposure has been the presence or absence of a smoking spouse. In our data set, no elevated risk was noted for this variable. Since our study was limited to women, part of the difference between our findings and those of earlier studies may be due to differences in the effects of passive smoke exposure by gender. The National Research Council's summary of 13 studies[21] found overall relative risks of lung cancer in nonsmokers due to spousal smoking of 1.32 for women and 1.62 for men (although the estimate for men was based on few cases). It is possible that men are exposed to other factors (e.g., occupational exposures) that may interact with passive smoke exposure to increase risk above that observed in women. Presence or absence of a smoking spouse is a relatively crude measure of passive smoke exposure, with a potential for wide variability in actual exposure. It was noted in one survey, for example, that 47% of women married to smokers reported zero hours of passive smoke exposure at home.[37] It has also been shown that considering spousal exposure alone may underestimate total household passive smoke exposure.[38] Another factor that may account for the differences in lung cancer risk due to spousal smoking between our study and earlier studies may be time trends in smoking patterns. The declining prevalence of smoking among men[39] has probably resulted in decreasing years and perhaps levels of exposure to passive smoke in the home among nonsmoking women whose husbands smoke.

Contrary to the findings of two earlier case-control studies,[7,26] our data showed no evidence of excess lung cancer risk due to passive smoke exposure in childhood. The risk of lung cancer due to childhood passive smoking may have some analogy to risk among ex-smokers. After 10 years of abstinence, the lung cancer risk for ex-smokers declines to 30% to 50% of the risk for continuing smokers.[40] Similarly, lung cancer risk due to passive smoke exposure in childhood may decline by adulthood, especially in the absence of adult-

TABLE 2—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Adulthood and Lung Cancer in Women, Missouri, 1986 through 1991

Source of Exposure	All Subjects[b]				Lifetime Nonsmokers			
	No. Cases	No. Controls	OR	95% CI	No. Cases	No. Controls	OR	95% CI
All household members								
Never	221	527	1.0		170	470	1.0	
Ever	394	873	1.0	0.8, 1.2	261	696	1.1	0.8, 1.3
Cigarette pack-years								
0	221	527	1.0		170	470	1.0	
>0–15	88	234	0.9	0.6, 1.2	56	181	0.9	0.6, 1.2
>15–40	91	261	0.8	0.6, 1.0	62	199	0.9	0.6, 1.2
>40	146	264	1.3	1.0, 1.6	107	217	1.3	1.0, 1.8
Cigarette pack-years x hours/day[c]								
0	221	527	1.0		170	470	1.0	
>0–50	90	261	0.8	0.6, 1.1	63	206	0.9	0.6, 1.2
>50–175	89	246	0.8	0.6, 1.1	58	189	0.9	0.6, 1.2
>175	124	238	1.2	0.9, 1.6	92	192	1.3	1.0, 1.8
Spouse only								
Never	287	650	1.0		213	568	1.0	
Ever	328	750	0.9	0.8, 1.1	218	598	1.0	0.8, 1.2
Cigarette pack-years								
0	287	650	1.0		213	568		
>0–15	58	166	0.7	0.5, 1.0	32	128	0.7	0.5, 1.1
>15–40	81	258	0.7	0.5, 0.9	54	200	0.7	0.5, 1.0
>40	150	266	1.2	0.9, 1.5	110	216	1.3	1.0, 1.7
Cigarette pack-years x hours/day[c]								
0	287	650	1.0		213	568	1.0	
>0–50	64	201	0.7	0.5, 0.9	41	161	0.7	0.5, 1.0
>50–175	81	237	0.7	0.5, 1.0	52	183	0.8	0.5, 1.1
>175	126	241	1.1	0.9, 1.5	94	193	1.3	1.0, 1.7

[a]Adjusted for age, history of previous lung disease, and active smoking (all subjects only).
[b]Includes lifetime nonsmokers and ex-smokers who had stopped at least 15 years before diagnosis or who had smoked for less than 1 pack-year.
[c]The product of total pack-years and average number of hours exposed per day to passive smoke in the home.

TABLE 3—Adjusted Odds Ratios (OR)[a] and 95% Confidence Intervals (CI) for the Relationship between Passive Smoke Exposure during Adulthood and Lung Cancer in Women, by Histologic Type, Missouri, 1986 through 1991

Source of Exposure	Adenocarcinoma			Other/Mixed			Squamous Cell			Small Cell		
	No. Cases	OR	95% CI	No. Cases	OR	95% CI	No. Cases	OR	95% CI	No. Cases	OR	95% CI
All household members												
Never	100	1.0		37	1.0		10	1.0		3	1.0	
Ever	192	1.1	0.8, 1.5	80	1.2	0.8, 1.8	16	0.7	0.3, 1.7	9	1.2	0.3, 4.5
Cigarette pack-years												
0	100	1.0		37	1.0		10	1.0		3	1.0	
>0–15	49	1.1	0.8, 1.6	17	1.0	0.5, 1.7	4	0.7	0.2, 2.2	1	0.5	0.0, 4.8
>15–40	48	0.9	0.6, 1.4	18	0.8	0.5, 1.6	5	0.7	0.2, 2.0	2	0.8	0.1, 4.8
>40	61	1.2	0.8, 1.7	31	1.5	0.9, 2.6	2	0.3	0.1, 1.4	5	2.2	0.5, 9.7
Spouse only												
Never	131	1.0		48	1.0		14	1.0		4	1.0	
Ever	161	1.0	0.8, 1.3	69	1.1	0.7, 1.7	12	0.6	0.3, 1.3	8	1.2	0.3, 4.1
Cigarette pack-years												
0	131	1.0		48	1.0		14	1.0		4	1.0	
>0–15	36	1.0	0.7, 1.6	10	0.7	0.4, 1.5	3	0.7	0.2, 2.4	1	0.7	0.1, 6.6
>15–40	41	0.8	0.5, 1.1	16	0.8	0.4, 1.4	6	0.8	0.3, 2.1	3	1.2	0.3, 5.6
>40	62	1.1	0.8, 1.5	34	1.6	1.0, 2.5	2	0.2	0.1, 1.1	4	1.7	0.4, 7.0

[a]Adjusted for age, history of previous lung disease, and active smoking.

hood exposure. In addition, there may be low reliability for quantitative measures (intensity and duration) of passive smoke exposure in childhood,[41,42] which makes assessment of lung cancer risk due to passive smoke exposure in childhood particularly difficult. Reliability and validity of measures of childhood exposure may be especially problematic when a large percentage of surrogate interviews are conducted (as in our study). Partially because of these limitations, few studies of child-

hood passive smoking and lung cancer have been conducted, and further research in this area is needed.

Our analyses by histologic type showed the largest increase in risk for other/mixed cell types and, although the estimate was based on very small numbers, for small cell carcinoma. Previous studies are inconsistent and often lacking in sample size when evaluating risk by cell type. Garfinkel et al.[10] found an elevated risk for squamous cell carcinoma and for other/mixed cell types. Others[5,18] have observed larger elevations for squamous and small cell carcinoma than for adenocarcinoma. In contrast, Wu et al.[11] and Fontham et al.[20] found larger increases for adenocarcinoma. An additional difficulty in evaluating previous studies of passive smoking and lung cancer by histologic type is that few studies have conducted systematic pathology reviews to verify cell type.

Our study has several major strengths. These include the large sample size—one of the largest series of nonsmoking lung cancer cases to date. In addition, we had relatively high response rates from both case patients and control subjects. Finally, we conducted a pathology review of cases.

The main limitation of our study is the possibility of recall bias for passive smoke exposure variables. The less quantitative measures of passive exposure (i.e., light, moderate, or heavy exposure) resulted in larger risk estimates than more quantitative estimates such as pack-years. Because there is no way to confirm previous passive smoke exposure, it is difficult to determine the best index for estimating exposure. However, we found that lung cancer risk due to adulthood passive smoke exposure was elevated at the highest quartile of exposure whether we used a more quantitative (e.g., pack-years) or less quantitative (e.g., heavy exposure) variable.

Another possible source of bias in our study is the large number of surrogate interviews for cases. Earlier studies,[38,43] however, have shown relatively close agreement on most passive smoke exposure variables as reported by subjects and spouses. We found fairly minor alterations in risk estimates when analyses were restricted to directly interviewed cases. In addition, we compared sociodemographic characteristics of direct and surrogate case-group interviews and found close agreement for most variables. As one might expect, the exception was age; there was a tendency toward more younger case patients in direct interviews.

In summary, our study and others conducted during the past decade suggest a small but consistent elevation in the risk of lung cancer in nonsmokers due to passive smoking. The proliferation of federal, state, and local regulations that restrict smoking in public places and work sites[44] is well founded. □

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